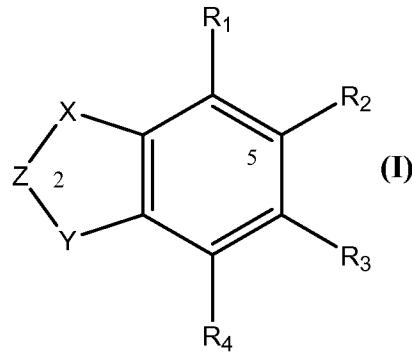


SECOND AMENDMENT AND RESPONSE TO OFFICE ACTION
U.S.S.N. 10/517,264

Claims Listing

1. (Currently amended) A method of inhibiting ~~cytokine or biological~~ activity of MIF comprising contacting MIF with ~~a cytokine or biological~~ an MIF activity-inhibiting effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof



wherein

X is—N(R₆)—;

Y is—N(R₇)—;

Z is—C(O)—;

R₁ is selected from hydrogen, or (CR₅R_{5'})_nhalo;

R₂ is selected from the group consisting of C₁-C₂₀alkyl, C₂-C₂₀alkenyl, C₂-C₂₀alkynyl, (CR₁₂R_{12'})_mC(O)R₈, (CR₁₂R_{12'})_mC(S)R₈, (CR₁₂R_{12'})_mS(O)R₈, (CR₁₂R_{12'})_mS(O)₂R₈, (CR₁₂R_{12'})_mOR₉, (CR₁₂R_{12'})_mSR₉, (CR₁₂R_{12'})_nNR₁₀R₁₁, (CR₁₂R_{12'})_mC(=NR₂₄)R₂₂ and (CR₁₂R_{12'})_mR₁₃;

R₃ is selected from hydrogen, C₁-C₆alkyl, (CR₁₆R_{16'})_pNR₁₄R₁₅, (CR₁₆R_{16'})_pOR₁₇, (CR₁₆R_{16'})_phalo, and (CR₁₆R_{16'})_pNO₂

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R₄ is hydrogen, or halogen;

Each R₅ and R₅ is independently hydrogen,

R₆ is hydrogen, or C₁-C₃alkyl;

R₇ is hydrogen or C₁-C₃alkyl;

R₈ is selected from the group consisting of hydrogen, C₁-C₂₀alkyl, C₂-C₂₀alkenyl, C₂-C₂₀alkynyl, OR₁₉, SR₁₉, N(R₂₀)₂, [NH—CH(R₂₁)—C(O)]_q—OR₂₉, pyranosyl and (CR₁₂R_{12'})_tR₁₃;

R₉ is hydrogen;

R₁₀ and R₁₁ are independently selected from hydrogen, and C(O)R₂₃;

Each R₁₂ and R_{12'} is independently hydrogen;

R₁₃ is selected from OR₂₅, SR₂₅, halo, N(R₂₅)₂, and C(O)R₃₁;

R₁₄ and R₁₅ are each hydrogen;

Each R₁₆ and R_{16'} is hydrogen;

R₁₇ is hydrogen;

R₁₉ and each R₂₀ are independently selected from hydrogen, C₁-C₂₀alkyl, and, (CR₂₆R_{26'})_tR₂₇;

R₂₁ is the characterising group of an amino acid wherein the amino acid is alanine, phenylalanine, serine, homoserine or norvaline;

R₂₂ is NH(C₁-₆alkyl);

R₂₃ is (CR₂₆R_{26'})_tR₂₇;

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Each R₂₄ is independently selected from hydrogen and C₁-C₆alkyl;

Each R₂₅ is independently selected from hydrogen, and C₁-C₆alkyl;

Each R₂₆ and R_{26'} is independently hydrogen;

R₂₇ is selected from, OR₃₀, SR₃₀, and aryl;

Each R₂₉ is independently selected from hydrogen and C₁-C₃alkyl;

Each R₃₀ is independently selected from, C₁-C₃alkyl, and heterocyclyl;

R₃₁ is heterocyclyloxy;

n is 0 or an integer from 1 to 3;

m is 0 or an integer from 1 to 20;

p is 0 or an integer from 1 to 6;

q is an integer from 1 to 5;

t is an integer from 1 to 10;

wherein alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

2. (Previously presented) A method according to claim 1 wherein X is—N(H)—, Y is—N(H)—, and Z is—C(O)—.

Claims 3 - 17 (Cancelled)

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18. (Original) A method according to claim 1 wherein the compound of formula 1 is selected from the group consisting of: benzimidazole-2-one-5-n-pentanoate, 5-[2-(1-oxy-2-hydroxyethyl)ethyl]benzimidazol-2-one-5-carboxylate, benzimidazole-2-one-5-methanoate, benzimidazole-2-one-5-ethanoate, 3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]tetrahydro-2H-pyran-2-yl-benzimidazole-2-one-5-carboxylate, 5-bromo-6-methylbenzimidazol-2-one, 5-hydroxy-6-methylbenzimidazol-2-one, 5-dodecanylbenzoimidazol-2-one, 4,5,7-tribromo-6-methylbenzimidazol-2-one, 4,5,6,7-tetrabromobenzimidazol-2-one, 5-methyl-6-nitrobenzimidazol-2-one, 5-amino-6-methylbenzimidazol-2-one, N-(6-methylbenzimidazol-5-yl)-2-pyrimidin-2-yl-sulfanyl-acetamide, pentyl-benzimidazol-2-one-5-carbothioate, 5-(benzimidazol-2(3H)-one-6-yl)-5-oxopentanoic acid, 2(3H)-benzimidazolone-5-sulfonic acid pentyl ester, 2(3H)-benzimidazolone-5-sulfonic acid pentyl amide, N-butyl-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboximidamide, 5-heptanoylbenzofuran-2(3H)-one, methyl 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoate, 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoic acid, methyl 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoate, 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoic acid, and N-(3,4-dihydroxyphenethyl)-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboxamide.

19. (Currently amended) A method of treating, ~~preventing or diagnosing a disease or condition~~ rheumatoid arthritis wherein MIF cytokine or biological activity is implicated comprising the administration of a treatment, ~~prevention~~ or diagnostic effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof to a

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subject in need thereof.

Claims 20-22. (cancelled)

23. (Original) A method of claim 19 wherein the subject is a human subject.

Claims 24-25. (cancelled)

26. (Currently amended) A method of treating ~~or preventing a disease or condition~~
rheumatoid arthritis wherein MIF ~~cytokine or biological~~ activity is implicated comprising:
administering to a mammal a compound of formula (I) as defined in claim 1 or a
pharmaceutically acceptable salt thereof and a second therapeutic agent.

27. (original) A method according to claim 26 wherein the second therapeutic agent is
a glucocorticoid.

28. (Currently amended) A method of ~~prophylaxis or treatment of a disease or~~
~~condition~~ rheumatoid arthritis for which treatment with a glucocorticoid is indicated, said
method comprising: administering to a mammal a glucocorticoid and a compound of formula (I)
as defined in claim 1 or a pharmaceutically acceptable salt thereof.

29. (Currently amended) A method of treating a steroid-resistant ~~disease or condition~~
rheumatoid arthritis comprising: administering to a mammal a glucocorticoid and a compound of

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formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

Claims 30-40. (Cancelled)

41. (Previously presented) A method according to claim 1 wherein

R₁ is hydrogen or (CR₅R_{5'})_nhalo;

R₂ is selected from C₁₋₂₀alkyl, (CR₁₂R_{12'})_mC(O)R₈, (CR₁₂R_{12'})_mS(O)₂R₈, (CR₁₂R_{12'})_nNR₁₀R₁₁, (CR₁₂R_{12'})_mC(=NR₂₄)R₂₂ and (CR₁₂R_{12'})_mR₁₃;

R₃ is selected from hydrogen, C₁₋₆alkyl, (CR₁₆R_{16'})_pNR₁₄R₁₅, (CR₁₆R_{16'})_pOR₁₇, (CR₁₆R_{16'})_phalo and (CR₁₆R_{16'})_pNO₂;

R₄ is hydrogen or halogen;

Each R₅ and R_{5'} is independently hydrogen;

R₈ is selected from C_{1-C₂₀}alkyl, OR₁₉, SR₁₉, N(R₂₀)₂, [NH-CH(R₂₁)-C(O)]_q-OR₂₉, pyranosyl and (CR₁₂R_{12'})R₁₃;

R₉ is hydrogen;

R₁₀ and R₁₁ are independently selected from hydrogen and C(O)R₂₃;

Each R₁₂ and R_{12'} is independently hydrogen;

R₁₃ is selected from OR₂₅, SR₂₅, halo, N(R₂₅)₂ and C(O)R₃₁;

R₁₄ and R₁₅ are each hydrogen;

Each R₁₆ and R_{16'} is hydrogen;

R₁₇ is hydrogen;

R₁₉ and each R₂₀ are independently selected from hydrogen, C_{1-C₂₀}alkyl, and (CR₂₆R_{26'})_tR₂₇;

R₂₁ is the characterising group of phenylalanine or serine;

R₂₂ is NH(C₁₋₆alkyl);

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R₂₃ is (CR₂₆R_{26'})_tR₂₇;

Each R₂₄ is independently selected from hydrogen and C₁-C₆alkyl;

Each R₂₅ is independently selected from hydrogen and C₁-C₆alkyl;

Each R₂₆ and R_{26'} is independently hydrogen;

R₂₇ is selected from OR₃₀, SR₃₀ and aryl;

Each R₂₉ is independently selected from C₁-C₃alkyl and heterocyclyl; and

R₃₁ is heterocyclyoxy.

42. (Previously presented) A method according to claim 41 wherein

n is 0;

m is 0;

p is 0;

q is 0; and

t is 1 or 2.

43. (Previously presented) A method according to claim 1 wherein the compound of formula (I) is benzimidazole-2-one-5-n-pentanoate.